PATENT SPECIFICATION

769,757

Date of Application and filing Complete Specification: May 11, 1955.
No. 13636/55.
Application made in United States of America on May 13, 1954.
Application made in United States of America on July 8, 1954.
Complete Specification Published: March 13, 1957.

Index at acceptance:—Class 2(3), C1B4, C1C(3: 5: 9: 11F), C2D43(B: C: D: S4).
International Classification:—C07d.

COMPLETE SPECIFICATION

Improvements in or relating to the Manufacture of Sulfonamides

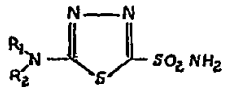
We, AMERICAN CYANAMID COMPANY, a corporation organised under the laws of the State of Maine, United States of America, of 30, Rockefeller Plaza, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the manufacture of 2-acylamino-1,3,4-thiadiazole - 5 - sulfonamides, which are useful as diuretic agents in the treatment of congestive heart failure and as agents for the treatment of glaucoma and epilepsy. As medicinal products they have many advantages, most notable of these being that they are non-toxic, non-mercurial, organic compounds which may be administered orally.

The compound 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide *per se* is claimed in our prior Specification No. 687,760.

The object of the present invention is to provide an improved process for synthesizing 2 - acylamino-1,3,4-thiadiazole-5-sulfonamides employing readily available starting materials.

The 2-acylamino-1,3,4-thiadiazole-5-sulfonamides have the following general formula:



wherein R_1 is an acyl radical and R_2 is then hydrogen: when R_1 and R_2 are taken together, they may form the phthaloyl radical. R_1, for example, may be a lower alkyl carbonyl radical such as propionyl, acetyl, trifluoroacetyl, butyryl, chloroacetyl or isovaleryl. R_1 may also be an aroyl substituent such as, for example, benzoyl; when R_1 and R_2 are taken together they may form the 1,2-phenylene dicarbonyl radical attached to the amino nitrogen on the 2-carbon atom.

The process in accordance with the invention comprises reacting 2-amino-1,3,4-thiadiazole-5-sulfonamide directly with the required carboxylic acid anhydride or acyl chloride.

When using an acid anhydride, since those commonly available are either liquids or low melting point solids, they may be conveniently reacted directly with the starting material—namely, 2-amino-1,3,4-thiadiazole - 5 - sulfonamide, without the presence of solvents. The 2 - acylamino-1,3,4-thiadiazole-5-sulfonamides form readily as solid precipitates. No acid acceptor is required during the course of the reaction, since the final product is readily separated from the acid side reaction products by simple filtration.

Althought it is possible for the reaction between the acid anhydride and the primary amine to take place at room temperature, such reaction is extremely slow due to the fact that the starting material used in the present invention is a weak base, thus requiring some heat to drive the acyl group on to the 2-amino-1,3,4-thiadiazole-5-sulfonamide. One exception may be cited to this general rule, namely that of trifluoroacetic anhydride which, being derived from a strong acid, reacts readily with the primary amine at room temperature. Generally, however, 100° C.—200° C. heat is required for the reaction to reach completion. We prefer to use a range of 140° C.—180° C. or the reflux temperature of the anhydride, if such is lower.

The reaction using an acid anhydride is substantially complete in a period of about 5 minutes to 1 hour, a range of about 15 minutes to 30 minutes usually being sufficient. Considerably longer periods of time may be required if the reaction is run at room temperature as, for example, in the case of the trifluoracetyl derivative, a period as long as 3½ hours may be required.

At the completion of the reaction, the product precipitates out readily upon cooling. The cooling step is employed since the product has a tendency to stay in solution when an excess of anhydride is used, the latter exerting a solvent effect upon the final product.

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In the reaction using an acyl chloride any readily available base may be used, provided it is capable of reacting with the acid liberated by the reaction i.e. acting as an acid acceptor. For this purpose we find pyridine, quinoline, triethylamine, tripropylamine and similar tertiary aliphatic amines to be suitable. Of this group we prefer to use pyridine. In addition, various inorganic bases such as the alkali metal hydroxides, carbonates and bicarbonates may be advantageously employed as acid acceptors in our process. Of this group we prefer to use the alkali metal hydroxides as neutralizing agents.

Upon formation of the 2-acylamino-1,3,4-thiadiazole-5-sulfonamide, the product is precipitated out in a suitable manner. When an organic base is used as the acid acceptor, the precipitation may be readily achieved by dilution with water. In cases where the inorganic base has been used however, and in particular, where the alkali metal hydroxide has been employed, acidification is necessary to effect precipitation. Any readily available organic or inorganic acid may be used for this purpose. For example, acetic, hydrochloric, sulfuric or phosphoric acids.

The product is preferably purified by recrystallization from water or aqueous-alcoholic mixtures. Alternatively it may be redissolved in an alkaline solution such as sodium hydroxide or potassium hydroxide and then reprecipitated with an organic or mineral acid such as acetic, hydrochloric, sulfuric, and phosphoric.

Acyl chlorides which may be used in this reaction are those containing lower alkyl, substituted lower alkyl, aryl or aralkoxy substituents. As for example, valeryl chloride, isovaleryl chloride, propionyl chloride, acetyl chloride, isobutyryl chloride, *n*-butyryl chloride, benzoyl chloride, chloroacetyl chloride, amino acetyl chloride and benzyloxycarbonyl chloride.

The reaction conditions which one may employ for our process may be varied between wide limits, depending upon the speed with which one desires to obtain the final product. The completeness of the reaction is therefore a function of temperature and time.

We prefer to carry out the process with no temperature controls. Upon addition of the acyl chloride to the 2-amino-1,3,4-thiadiazole-5-sulfonamide, an exothermic reaction takes place. The reaction mixture is then heated for a period of about 15 minutes to about 3 hours, preferably about 30 minutes, at reflux temperature. This treatment enhances the rate of the reaction considerably and is not deleterious to the yield of product. If desired, however, the heating step may be omitted, in which case a somewhat longer period is required for the reaction to reach completion.

An alternative method for controlling the rate of the reaction is to maintain a temperature of about 15° C. to 50° C., preferably about 25° C. Obviously, this results in a slower reaction rate, although the ultimate yields of product is not adversely affected. If so desired, extremely mild conditions may be maintained. In this case the temperature is maintained in the order of $-10°$ C. to $+10°$ C., preferably about 0° C. In such cases, the rate of reaction is extremely slow, requiring as long as one or two days to reach completion.

The products of this invention are white crystalline compounds having a relatively high melting point range, namely about 220—290° C. They are very slightly soluble in water or acids, sparingly soluble in organic solvents and soluble in organic and inorganic bases.

Specific examples illustrating the process of the invention will now be set forth. All parts are by weight unless otherwise indicated.

Example I.

A 19.5 cc. (0.15 mole) sample of propionic anhydride was heated to 125° C. and 10 g. (0.055 mole) of 2-amino-1,3,4-thiadiazole-5-sulfonamide was added portionwise with stirring during 20 minutes. The reaction mixture was then heated to 140° C. for 30 minutes and cooled. The product, 2-propionylamino-1,3,4-thiadiazole-5-sulfonamide, which separated out, was filtered off and recrystallized from 45 cc. of hot water. The product has a melting point of 247—248° C. dec., is soluble in dilute alkali, in dilute acid and has a pK_{a_1} equal to 7.1 and a pK_{a_2} equal to 8.3.

Example II.

A 14.1 ml. (0.15 mole) portion of acetic anhydride was heated to 110° C. and 10 g. (0.055 mole) of 2-amino-1,3,4-thiadiazole-5-sulfonamide was added portionwise over 20 minutes, with stirring. The mixture was then boiled under reflux for 30 minutes and cooled. The precipitated product was filtered off and recrystallized from hot water, yielding 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide having a melting point of 259° C., dec.

Example III.

A 1.0 g. (0.0055 mole) portion of 2-amino-1,3,4-thiadiazole-5-sulfonamide was added portionwise to 3.5 ml. (0.06 mole) of trifluoroacetic anhydride with shaking and occasional cooling. The mixture was allowed to stand for 3½ hours at room temperature. The solid was filtered and dried yielding 2-trifluoroacetylamino-1,3,4-thiadiazole-5-sulfonamide which was purified by dissolving in ether and precipitating by the addition of petroleum ether. The product has a melting point of 220—221° C., dec

Example IV.

An intimate mixture of 4.0 g. (0.028 mole) of phthalic anhydride and 5.05 g. (0.028 mole) of 2-amino-1,3,4-thiadiazole-5-sulfonamide was heated at 180—190° C. for 20 minutes.

The mixture was cooled and the product purified by extraction with ethyl acetate and recrystallization from glacial acetic acid yielding 2-phthaloylamino-1,3,4-thiadiazole - 5-sulfonamide having a melting point of 275—277° C. dec.

EXAMPLE V.

A 24.2 ml. (0.51 mole) portion of *n*-butyric anhydride was heated to 125° C. and 10 g. (0.055 mole) of 2-amino-1,3,4-thiadiazole-5-sulfonamide was added portionwise over 20 minutes with stirring. The mixture was heated at 150° C. for 30 minutes and cooled. The product 2-*n*-butyrylamino-1,3,4-thiadiazole-5-sulfonamide was filtered off and recrystallized from hot water. Melting point 260—262° C., dec..

EXAMPLE VI.

A mixture of 5.1 g. (0.02 mole) of chloroacetic anhydride and 3.6 g (0.02 mole) of 2-amino - 1,3,4-thiadiazole - 5-sulfonamide was heated at 150° C. for 15 minutes. The mixture was cooled and the product filtered off and washed with ether and petroleum ether. It was recrystallized from hot water for purification yielding 2 - chloroacetylamino - 1,3,4-thiadiazole-5-sulfonamide having a melting point of 236—240° C., dec.

EXAMPLE VII.

A mixture of 19 g. (0.10 mole) of isovaleric anhydride and 10 g. (0.05 mole) of 2-amino-1,3,4-thiadiazole-5-sulfonamide was heated at 150—160° C. for 30 minutes with stirring. The mixture was cooled and filtered and the product washed with ether. It was recrystallized from hot water for purification yielding 2-isovalerylamino - 1,3,4-thiadiazole - 5-sulfonamide having a melting point of 246—248° C., dec.

EXAMPLE VIII

A mixture of 22.6 g. (0.10 mole) of benzoic anhydride and 10 g. (0.055 mole) of 2-amino-1,3,4-thiadiazole-5-sulfonamide was heated at 150—160° C. for 30 minutes. It was cooled and shaken with ether. The product was filtered off, washed with ether and recrystallized from hot water yielding 2-benzoylamino-1,3,4-thiadiazole-5-sulfonamide having a melting point of 277—279° C., dec.

EXAMPLE IX.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was suspended in 12 cc. of pyridine and 2.40 grams (0.02 mole) of isovaleryl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid material dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate the product. This solid was crystallized first from 400 cc. and then from 300 cc. of hot water to give 2-isovaleryl-amino - 1,3,4-thiadiazole-5-sulfonamide, melting at 246—248° C. dec. and having a $pK_{a_1} = 7.2$ and a $pK_{a_2} = 8.6$. The material is soluble in dilute alkali and insoluble in dilute acid.

EXAMPLE X.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole-5-sulfonamide was suspended in 12 cc. of pyridine and 1.86 grams (0.02 mole) of propionyl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate 2-propionylamino-1,3,4-thiadiazole-5-sulfonamide. This product was filtered off and recrystallized from hot water. The pure material melts at 147—148° C. dec., is soluble in dilute alkali, insoluble in dilute acid and has a $pK_{a_1} = 7.1$ and a $pK_{a_2} = 8.3$.

EXAMPLE XI.

A 3.60 gram (0.02 mole) sample of 2-amino - 1,3,4-thiadiazole - 5-sulfonamide was suspended in 12 cc. of pyridine and 1.58 grams (0.02 mole) of acetyl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid material dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate 2-acetylamino-1,3,4-thiadiazole-5- sulfonamide. The material was crystallized from hot water to give the pure compound as a white, crystalline solid melting at 259° C. dec.

EXAMPLE XII.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole-5-sulfonamide was suspended in 12 cc. of pyridine and 2.13 grams (0.02 mole) of isobutyryl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid material dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate 2-isobutyrylamino-1,3,4-thiadiazole - 5-sulfonamide. This solid was crystallized from two 250 cc. portions of hot water to give a product melting at 280—283° C. dec. and having a $pK_{a_1} = 7.1$ and a $pK_{a_2} = 8.6$.

EXAMPLE XIII.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was suspended in 12 cc. of pyridine and 2.13 grams (0.02 mole) of *n*-butyryl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid material dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate 2-*n*-butyrylamino - 1,3,4 - thiadiazole - 5 - sulfonamide. This material was crystallized from tallization from water, to yield a product having a melting point of 260—262° C. dec.

EXAMPLE XIV.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was suspended in 12 cc. of pyridine and 2.81 grams (0.02 mole) of benzoyl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid material dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate 2-benzoylamino - 1,3,4 - thiadiazole - 5 - sulfonamide. This material was crystallized from water to give a product melting at 277—279° C. dec.

EXAMPLE XV.

A 3.60 gram (0.02 mole) sample of 2-amino - 1,3,4-thiadiazole - 5-sulfonamide was suspended in 12 cc. of pyridine and 4.55 grams (0.02 mole) of N-(carbobenzoxy)glycyl chloride was added dropwise with stirring. An exothermic reaction occurred and all of the solid material dissolved. The reaction mixture was heated at 100° C. for a half hour longer and poured onto crushed ice to precipitate 2-[(N-carbobenzoxy)glycylamino] - 1,3,4-thiadiazole-5-sulfonamide melting at 215—216° C.

EXAMPLE XVI.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5 - sulfonamide was suspended in 12 cc. of pyridine and 2.26 grams (0.02 mole) of chloroacetylchloride was added dropwise with stirring. An exothermic reaction occurred and all the solid material dissolved. The reaction mixture was then heated at 100° C. for 30 minutes longer and poured onto crushed ice to precipitate 2-chloroacetylamino - 1,3,4-thiadiazole - 5-sulfonamide. The product was purified by recrystallization from hot water and melted at 236—240° C. dec.

EXAMPLE XVII.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. Benzoyl chloride in the amount of 2.81 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then added simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2-benzoylamino-1,3,4-thiadiazole - 5-sulfonamide as a heavy white solid having a melting point of 245—253° C. dec. The compound was purified by recrystallization from a large volume of water; melting point 277—279° C. dec.

EXAMPLE XVIII.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. Acetyl chloride in the amount of 1.58 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then added simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2-acetylamino - 1,3,4-thiadiazole - 5-sulfonamide. After recrystallization from water the product is obtained as a colorless crystalline solid melting at 259° C. dec.

EXAMPLE XIX.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. Chloroacetyl chloride in the amount of 2.26 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then added simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2 - chloroacetylamino - 1,3,4 - thiadiazole - 5-sulfonamide. The product was purified by recrystallization from hot water and melted at 236—240° C. dec.

EXAMPLE XX.

A. 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. Isovaleryl chloride in the amount of 2.40 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then added simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2-isovalerylamino-1,3,4-thiadiazole-5-sulfonamide. The product was crystallized from hot water, melting at 246—248° C. dec.

EXAMPLE XXI.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. Propionyl chloride in the amount of 1.86 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then aded simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to

precipitate 2-propionylamino-1,3,4-thiadiazole-5-sulfonamide. The product was filtered and recrystallized from hot water. The material melts at 147—148° C. dec.

EXAMPLE XXII.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. Isobutyryl chloride in the amount of 2.13 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then added simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2-isobutyrylamino-1,3,4-thiadiazole-5-sulfonamide. The material was recrystallized from two 250 cc. portions of hot water to give a product melting at 280—283° C. dec.

EXAMPLE XXIII.

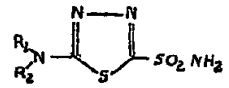
A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5-sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. *n*-butyryl chloride in the amount of 2.13 grams (0.02 mole) and 4 cc. of 5N sodium hydroxide (0.02 mole) were then added simultaneously with cooling and stirring. After about 15 minutes the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2-*n*-butyrylamino - 1,3,4 - thiadiazole-5-sulfonamide. The material was purified by crystallization from water, melting at 260—267° C. dec

EXAMPLE XXIV.

A 3.60 gram (0.02 mole) sample of 2-amino-1,3,4-thiadiazole - 5 - sulfonamide was dissolved in 8 cc. of 2.5N sodium hydroxide (0.02 mole) and the solution was cooled to 0° C. to −10° C. N-(Carbobenzoxy)glycyl chloride in the amount of 4.55 grams and 4 cc. of 5N sodium hydroxide were then added simultaneously with cooling and stirring. After about 15 minutes, the cooling bath was removed and stirring was continued at room temperature for 45 minutes. The reaction mixture was then extracted with ether and acidified with hydrochloric acid to precipitate 2-[(N-carbobenzoxy)glycylamino]-1,3,4-thiadiazole-5-sulfonamide. The compound was purified by recrystallization from a large volume of water.

What we claim is:—

1. A method of preparing 2-acylamino-1,3,4 - thiadiazole - 5 - sulfonamides of the formula



wherein R_1 is an acyl radical and R_2 is then hydrogen, and when R_1 and R_2 are taken together they form the phthaloyl radical, which comprises reacting 2-amino-1,3,4-thiadiazole-5-sulfonamide with the required carboxylic acid anhydride or acyl chloride.

2. A method according to claim 1, in which the reaction is carried out at a temperature of 100° C. to 200° C., and preferably 140° C. to 180° C., in the absence of a solvent, when an acid anhydride is used.

3. A method according to claim 1, in which the reaction is carried out in the presence of an acid acceptor, preferably without temperature control, when an acyl chloride is used.

4. A method of preparing 2-acylamino-1,3,4-thiadiazole-5-sulfonamides substantially as hereinbefore described.

5. 2-Acylamino - 1,3,4-thiadiazole-5-sulfonamides whenever prepared by the method according to any of the preceding claims.

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Chartered Patent Agents,
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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1957.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.